

Listing of Claims:

Claim 1. (original) A drug discovery process for identification of a small organic compound that is able to bind to a biological target molecule, the process comprising mutating a biological target molecule in such a way that at least one amino acid residue capable of binding a metal ion is introduced into the biological target molecule so as to obtain a metal ion binding site as an anchor point in the mutated biological target molecule.

Claim 2. (original) A drug discovery process according to claim 1 further comprising

- (a) contacting the mutated biological target molecule with a test compound which comprises a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of the test compound to the introduced metal ion binding site of the mutated biological target molecule, and
- (b) detecting any change in the activity of the mutated biological target molecule or determining the binding affinity of the test compound to the mutated biological target molecule.

Claim 3. (original) A drug discovery process according to claim 1 further comprising

- (a) contacting the mutated biological target molecule with one or more members of a library of test compounds that comprise a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of at least a member of the library of test compounds to the introduced metal ion binding site of the mutated biological target molecule, and
- (b) detecting any change in the activity of the mutated biological target molecule or determining the binding affinity of the test compound to the mutated biological target molecule.

Claim 4. (original) A drug discovery process for identification of a small organic compound that is able to bind to a biological target molecule which has at least one metal ion binding site, the process comprising

(a) contacting the biological target molecule with a test compound which comprises a moiety including at least two heteroatoms for etiolating a metal ion, under conditions permitting non-covalent binding of the test compound to the metal ion binding site of the biological target molecule, and

(b) detecting any change in the activity of the biological target molecule or determining the binding affinity of the test compound to the biological target molecule.

Claim 5. (original) A drug discovery 'process for identification of a small organic compound that is able to bind to a biological target molecule which has at least one metal ion binding site, the process comprising

(a) contacting the biological target molecule with one or more members of a library of test compounds that comprise a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of at least a member of the library of test compounds to the metal ion binding site of the biological target molecule, and

(b) detecting any change in the activity of the biological target molecule or determining the binding affinity of the test compound to the biological target molecule.

Claim 6. (currently amended) A drug discovery process according to claim 1 ~~any~~ of ~~claims 1-5~~ further comprising

(c) identifying the test compound that non-covalently binds to the biological target molecule.

Claim 7. (currently amended) A drug discovery process according to claim 1 ~~any of claims 1—3 or 6~~ further comprising

(d) selecting two or more test compounds capable of forming a non-covalent binding to a biological target molecule, and capable of changing the activity of the biological target molecule or the binding affinity of the test compound to the biological target molecule to form a library of test compounds.

Claim 8. (currently amended) A drug discovery process according to claim 1 ~~any of claims 1—3 or 6~~ further comprising

(e) contacting the biological target molecule in wild-type, non-mutated form with at least one test compound determined to non-covalently bind the mutated biological target molecule in step (a), and

(f) detecting any change in the activity of the biological target molecule or determining the binding affinity of the test compound to the biological target molecule.

Claim 9. (currently amended) A drug discovery process according to claim 1 ~~any of claims 1—3 or 6~~ further comprising

(e) contacting the biological target molecule in wild-type, non-mutated form with two or more members of a library of test compounds, wherein the test compounds in chelated form have been determined to non-covalently bind the mutated biological target molecule in step (a), and

(f) detecting any change in the activity of the biological target molecule or determining the binding affinity of the test compound to the biological target molecule.

Claim 10. (previously presented) A drug discovery process according to claim 8 further comprising

(g) identifying the test compound that interacts with the wild-type biological target molecule.

Claim 11. (currently amended) A drug discovery process according to claim 1 ~~any of claims 1—3 or 6~~ further comprising

(e) contacting the biological target molecule in wild type, non mutated form with at least one test compound determined to non-covalently bind the mutated or non-mutated biological target molecule in step (a) but lacking a metal ion chelated thereto, and

(f) detecting any change in the activity of the biological target molecule or determining the binding affinity of the non-chelated test compound to the biological target molecule.

Claim 12. (currently amended) A drug discovery process according to claim 1 ~~any of claims 1—3 or 6~~ further comprising

(e) contacting the biological target molecule in wild-type, non-mutated form with two or more members of a library of non chelated test compounds, wherein the test compounds in chelated form have been determined to non-covalently bind the mutated or non-mutated biological target molecule in step (a), and

(f) detecting any change in the activity of the biological target molecule or determining the binding affinity of the non-chelated test compound to the biological target molecule.

Claim 13. (currently amended) A drug discovery process according to claim 1 ~~claims 11~~ further comprising

(g) identifying the non-chelated test compound that interacts with the wild-type biological target molecule.

Claim 14. (previously presented) A drug discovery process according to claim 8 further comprising

(a) identification of any binding or interaction between the non-chelated test compound and the wild-type biological target molecule.

Claim 15. (currently amended) A drug discovery process according to claim 1 ~~any of claims 1—3 or 6~~, wherein the biological target molecule is a protein.

Claim 16. (original) A drug discovery process according to claims 15, wherein the protein comprises an amino acid residue and wherein the metal ion binding site in the protein is introduced by amino acid substitution at or in the vicinity of

- 1) a site where the binding of the test compound will interfere with the binding to another protein, for example a regulatory protein, or to a domain of the same protein;
- 2) a site where the binding of the test compound will interfere with the cellular targeting of the protein;
- 3) a site where the binding of the test compound will directly or indirectly interfere with the binding of substrate or the binding of an allosteric modulatory factor for the protein;
- 4) a site where the binding of the test compound may interfere with the intra-molecular interaction of domains within the protein, for example the interaction of a regulatory domain with a catalytic domain;
- 5) a site where binding of the test compound will interfere with the folding of the protein, for example the folding of the protein into its active conformation; or
- 6) a site where the binding of the test compound will control the activity of the protein, for example by an allosteric mechanism.

Claim 17. (previously presented) A drug discovery process according to claim 15, wherein the metal ion binding amino acid residue in the biological target molecule is introduced by site-directed mutagenesis.

Claim 18. (previously presented) A drug discovery process according to claim 15, wherein the mutated biological target molecule is obtained as a recombinant expression product in purified or non purified form.

Claim 19. (currently amended) A drug discovery process according to claim 1, wherein the mutated biological target molecule is obtained as a synthetic or semi-synthetic product.

Claim 20. (currently amended) A drug discovery process according to claim 15, wherein step (a) ~~in any of claims 2 or 3~~ comprises the further step of determining, based on the three-dimensional structure of the specific protein in question or the primary structure of the specific protein together with a three-dimensional model of the class of proteins to which the specific protein belongs, the location of the metal ion binding amino acid residue in the mutated or non-mutated protein, and determining the location of at least one other amino acid residue in the vicinity of the metal ion binding amino acid residue.

Claim 21. (currently amended) A drug discovery process according to claim 15, wherein the binding of the test compound to the mutated or non-mutated protein in step (a) ~~in any of claims 2 or 3~~ is determined using detection of any changes in the biological activity of the protein, competition with binding of a labelled ligand of the protein, or using a metal ion chelator which is in itself detectable or labelled with a detectable labelling agent.

Claim 22. (original) A drug discovery process according to claim 19, wherein the amino acid residue in the vicinity of the metal ion binding amino acid residue is one which is

capable of directly or indirectly binding at least one functional group of the test compound other than the metal ion.

Claim 23. (original) A drug discovery process according to claim 22, wherein the amino acid residue capable of binding at least one functional group of the test compound other than the metal ion is detected using site-directed mutagenesis of at least one amino acid residue of the protein potentially involved in interaction with said functional group of the test compound other than the metal ion, followed by expression of the mutated protein in a suitable cell, contacting said cell or a portion thereof including the mutated protein with the test compound, and detecting any changes in the activity of the protein, determining any effect on binding in a competitive binding assay using a labelled ligand of the protein, or using a chelating agent which is in itself detectable or labelled with a detectable labelling agent.

Claim 24. (original) A drug discovery process according to claim 22, wherein the amino acid residue capable of binding at least one functional group of the test compound other than the metal ion is detected by structural analysis employing i) a process involving crystallisation followed by X-ray, or ii) a process involving NMR.

Claim 25. (currently amended) A drug discovery process according to claim 15, wherein step (a) comprises the further steps of improving the binding affinity of a metal ion chelate to the mutated or non mutated protein, the method comprising

- (i) selecting a metal ion chelate with an activity to or a binding affinity to the mutated protein of 50 pM or better ~~as identified by the method of claim 21,~~
- (ii) mapping the site of the protein to which the chelate binds ~~using the method of claim 20, 23 and/or 24,~~
- (iii) optionally locating at least one amino acid residue in the vicinity of the chelate,

- (iv) altering one or more functional group of the chelate to optimise for direct or indirect interaction with said amino acid residue to generate a library of chelate derivatives,
- (v) screening the derivatives of step (iv) ~~by the method of claim 21,~~
- (vi) selecting metal ion chelates having at least a two fold increase in activity or in binding affinity,
- (vii) optionally repeating any one or a combination of two or more of steps (i)-(vi) one or more times to generate metal ion chelating compounds with an improved binding affinity for the mutated or non-mutated protein, and
- (viii) optionally screening the thus selected metal ion chelates for binding to the wild type protein ~~by the method of claim 21,~~
- (ix) optionally selecting metal ion chelates having at least an activity or a binding affinity to the wild: type protein of 50 pM or better ~~as identified by the method of claim 21,~~ and
- (x) optionally repeating any one or a combination of two or more of steps (vii)-(ix) one or more times to generate metal ion chelating compounds with an improved binding affinity for the wild-type protein.

Claim 26. (previously presented) A drug discovery process according to claim 15, wherein step (e) comprises the further steps of generating a library of test compounds which are derivatives of a test compound found to interact with the wild type protein in step (e), each test compound in the library being provided with at least one functional group for direct or indirect interaction with at least one amino acid of the wild-type protein, which functional group differs from at least one functional group of each of the other test compounds, and screening the test compound library for compounds interacting with the wild-type protein.

Claim 27. (previously presented) A drug discovery process according to claim 15, wherein step (e) is performed by detecting any changes in the activity of the protein, detecting

an effect on binding in a competitive binding assay using a labelled ligand of the protein, or using a chelating agent which is in itself detectable or labelled with a detectable labelling agent.

Claim 28. (currently amended) A drug discovery process according to claim 15, wherein step (e) comprises the further step of determining - based on the three-dimensional structure of the specific protein in question or the primary structure of the specific protein together with the three-dimensional model of the class of proteins to which the specific protein belongs, and based on the information ~~provided by the method of claim 25~~ of the location of amino acid residues in the vicinity of the metal ion binding residue introduced in the mutated protein - the location of an amino acid residue in the wild-type protein binding at least one functional group of a test compound.

Claim 29. (original) A drug discovery process according to claim 28, wherein the amino acid residue capable of binding at least one functional group of the test compound is detected using site-directed mutagenesis of at least one amino acid residue of the wild-type protein potentially involved in interaction with said functional group of the test compound, followed by expression of the mutated protein in a suitable cell, contacting said cell or a portion thereof including the mutated protein with the test compound, and determining any effect on binding using detection of any changes in the biological activity of the protein, a competitive binding assay using a labelled ligand of the protein, or using a chelating agent which is in itself detectable or labelled with a detectable labelling agent.

Claim 30. (original) A drug discovery process according to claim 28, wherein the amino acid residue capable of binding at least one functional group of the test compound other than the metal in is detected by structural analysis employing i) a process involving crystallisation followed by X-ray, or ii) a process involving NMR.

Claim 31. (currently amended) A drug discovery process according to claim 1 ~~any of claims 1-3 or 6~~, wherein the biological target molecule is selected from the

group consisting of proteins, polypeptides, oligopeptides, nucleic acids, carbohydrates, nucleoproteins, glycoproteins, glycolipids, lipoproteins and derivatives thereof.

Claim 32. (original) A drug discovery process according to claim 31, wherein the biological target molecule is a protein selected from the group consisting of membrane receptors, signal transduction proteins, scaffolding proteins, nuclear receptors, steroid receptors, intracellular receptors, transcription factors, enzymes, allosteric enzyme regulator proteins, growth factors, hormones, neuropeptides or immune globulins.

Claim 33. (original) A drug discovery process according to claim 32, wherein the protein is a membrane protein.

Claim 34. (original) A drug discovery process according to claim 33, wherein the biological target molecule is a membrane protein and the metal ion binding site in the biological target molecule is introduced in a ligand binding crevice of the membrane protein.

Claim 35. (original) A drug discovery process according to claim 33, wherein the membrane protein is an integral membrane protein.

Claim 36. (original) A drug discovery process according to claim 35, wherein the membrane protein comprises 1-14 transmembrane domains such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 domains.

Claim 37. (original) A drug discovery process according to claim 36, wherein the membrane protein is a receptor such as a tyrosine kinase receptor, e.g. a growth factor receptor such as the growth hormone, insulin, epidermal growth factor, transforming growth factor, erythropoietin, colony-stimulating factor, platelet-derived growth factor receptor or nerve growth factor receptor (TrkA or TrkB).

Claim 38. (original) A drug discovery process according to claim 36, wherein the membrane protein is a purinergic ion channel,

Claim 39. (original) A drug discovery process according to claim 36, wherein the membrane protein is a ligand-gated ion channel, such as a nicotinic acetylcholine receptor, GABA receptor, or glutamate receptor (NMDA or AMPA).

Claim 40. (original) A drug discovery process according to claim 36, wherein the membrane protein is a voltage-gated ion channel, such as a potassium, sodium, chloride or calcium channel.

Claim 41. (original) A drug discovery process according to claim 36, wherein the membrane protein is a 7TM receptor, a G-protein coupled receptor, such as the acetylcholine receptors, ACTH receptors, adenosine receptors, adrenoceptors, anaphylatoxin chemotactic receptor, angiotensin receptors, bombesin (neuromedin) receptors, bradykinin receptors, calcitonin and calcitonin gene related peptide receptors, conopressin receptors, corticotropin releasing factor receptors, amylin receptors, adrenomedullin receptors, calcium sensors, cannabinoid receptors, CC-chemokine receptors, cholecystoldnin receptors, dopamine receptors, eicosanoid receptors, endothelin receptors, fMLP receptors, GABA_B receptors, galanin receptors, gastrin receptors, gastric inhibitory peptide receptors, glucagons receptors, glucagon-like I and II receptors, glutamate metabotropic receptors, glycoprotein hormone (e.g. FSH, LSH, TSH, LH) receptors, gonadotropin releasing hormone receptors, growth hormone releasing hormone receptors, growth hormone releasing peptide (Ohrelin) receptors, histamine receptors, 5-hydroxytryptamine receptors, leukotriene receptors, lysophospholipid receptors, melanocortin receptors, melanin concentrating hormone receptors, melatonin receptors, melanocortin receptors, neuropeptide Y receptors, neurotensin receptors, odor component receptors, opioid and opioid-like receptors, retinal receptors (opsins), orexin receptors, oxytocin receptors, parathyroid hormone and parathyroid hormone-related peptide receptors, P2Y receptors, pheromone receptors, platelet activating factor receptors, prostanoid receptors, protease-activated

receptors, secretin receptors, somatostatin receptors, tachykinin receptors, thyrotropin-releasing hormone receptors, pituitary adenylate activating peptide receptors, vasopressin receptors, vasoactive intestinal peptide receptors and virally encoded 7TM receptors; in particular galanin receptors, P2Y receptors, chemokine receptors, metabotropic glutamate receptors, melanocortin receptors, bombesin receptors, cannabinoid receptors, lysophospholipid receptors, IMLP receptors, neuropeptide Y receptors, tachykinin receptors, dopamine receptors, histamine receptors, 5-hydroxytryptamine receptors, histamine receptors, mas proto-oncogene, acetylcholine, oxytocin, herpes virus encoded 7TM receptors, epstein-barr virus induced 7TM receptors, cytomegalovirus encoded receptors and bradykinin receptors; preferably galanin receptor type 1, leukotriene B4 receptor CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CX3CR1, mGLU-R1, mGLU-R2, m-GLU-R3, m-GLU-R4, m-GLU-R5, m-GLU-R6, m-GLU-R8, melanin concentration hormone receptors, melanocortin-1 receptor, melanocortin-3 receptor, melanocortin-4 receptor, melanocortin-5 receptor, bombesin receptor subtype 3, cannabinoid receptor 1, cannabinoid receptor 2, EDG-2, EDG-4, FMLP-related receptor I, FMLP-related receptor II, NPY Y6 receptor, NPY Y5 receptor, NPY Y4 receptor, NK-1 receptor, NTC-3 receptor, D2 receptor (short), D2 receptor (long), Duffy antigen, U27, U28, UL33 and U78 from human cytomegalovirus, U12 and U51 from human herpes virus 6A, 6B or 7, ORF-74 from human herpes virus 8, Epstein Barr virus induced receptor -2, histamine H1 receptor, MAS protooncogene, muscarinic M1 receptor, muscarinic M2 receptor, muscarinic M3 receptor, muscarinic M5 receptor, oxytocin receptor, XCR1 receptor, RDC1 receptor, GPR12 receptor or GPR3 receptor.

Claim 42. (original) A drug discovery process according to claim 36, wherein the membrane protein is a. transporter protein, such as a GABA, monoamine, glutaminic acid or nucleoside transporter.

Claim 43. (original) A drug discovery process according to claim 36, wherein the membrane protein is a multidrug resistance protein, e.g. a P-glycoprotein, multidrug resistance

associated protein, drug resistance associated protein, lung resistance related protein, breast cancer resistance protein, adenosine triphosphate-binding cassette protein, Bmr, QacA or EmrAB/TolC pump.

Claim 44. (original) A drug discovery process according to claim 36, wherein the membrane protein is a cell adhesion molecule, e.g. NCAM, VCAM or ICAM.

Claim 45. (original) A drug discovery process according to claim 36, wherein the membrane protein is an enzyme such as adenylyl cyclase.

Claim 46. (original) A drug discovery process according to claim 35, wherein the membrane protein is an orphan receptor.

Claim 47. (original) A method of identifying a metal ion binding site in a biological target molecule, the method comprising

(a) contacting the biological target molecule with a test compound which comprises a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of the test compound to the biological target molecule, and

(b) detecting any change in the activity of the biological target molecule or determining the binding affinity of the test compound to the biological target molecule.

Claim 48. (original) A method of identifying a metal ion binding site in a protein, the method comprising

(a) analysing the nucleotide sequence of the gene coding for the protein in order to deduce the amino acid sequence,

(b) building a molecular model of the protein or a part of the protein based on the deduced amino acid sequence and the generic three-dimensional model of the 30 class of proteins to which the specific protein belongs,

(c) identifying the presence of amino acid residues such as, e.g., histidine, cysteine and/or aspartate residues, capable of binding a metal ion and located in suitable relative positions.

Claim 49. (previously presented) A method according to claim 47, wherein the test compound is contacted with two or more biological target molecules for identification of possible metal ion binding sites thereof.

Claim 50. (original) A method of identifying a metal ion binding site in a protein, the method comprising

- (a) selecting a nucleotide sequence suspected of coding for a protein and deducing the amino acid sequence thereof,
- (b) expressing said nucleotide sequence in a suitable host cell,
- (c) contacting said cell or a portion thereof including the expressed protein with a test compound which comprises a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of the test compound to the protein, and detecting any change in the activity of the protein or determining the binding affinity of the test compound to the protein; and
- (d) determining, based on the generic three-dimensional model of the class of proteins to which the protein or suspected protein belongs, at least one metal ion binding amino acid residue located in said protein to locate the metal ion binding site of said protein.

Claim 51. (original) A method of mapping a metal ion binding site of a protein, the method comprising

- (a) contacting the protein with a test compound which comprises a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of the test compound to the protein, and detecting any change in the activity of the protein or determining the binding affinity of the test compound to the protein, and

(b) determining, based on the primary structure of the specific protein in question and the generic three-dimensional model of the class of proteins to which the specific protein of step (a) belongs, at least one metal ion binding amino acid residue located in the membrane protein to identify the metal ion binding site of said membrane protein.

Claim 52. (cancelled)

Claim 53. (currently amended) A drug discovery process according to claim 1, wherein the test compound has a log K value in a range of from about 3 to about 18 ~~such as, e.g. from about 3 to about 15, from about 3 to about 12, from about 4 to about 10, from about 4 to about 8, from about 4.5 to about 7, from about 5 to about 6.5 such as from about 5.5 to about 6.5.~~

Claim 54. (currently amended) A drug discovery process according to claim 1, wherein the test compound forms a chelate with a metal ion selected from the group consisting of Co, Cu, Ni, Pt and Zn including the various oxidation steps such as, e.g., Co (II), Co (III), Cu (I), Cu (II), Ni (II), Ni (III), Pt (II), Pt (IV) and Zn (II).

Claim 55. (currently amended) A drug discovery process according to claim 1, wherein the test compound has at least two heteroatoms, similar or different, selected from the group consisting of nitrogen (N), oxygen (O), sulfur (S), selenium (Se) and phosphorous (P).

Claim 56. (currently amended) A drug discovery process according to claim 1, wherein the test compound has the general formula I



(X)

wherein F is N, O, S, Se or P; and G is N, O, S, Se or P;

at least one of (X)_n and (Y)_m is present and if n is 0, then -(X)_n - is absent, and if m is 0, then -(Y)_m - is absent, and both n and m are not 0;

RI and R2, which are the same or different, are radicals preferably selected from the group consisting of: hydrogen, a C1-C15 alkyl, C2-C15 alkenyl, C2-C15 alkynyl, aryl, cycloalkyl, alkoxy, ester, -OOR', -COOR', heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl or heteroaryl group, an amine, imine, nitro, cyano, hydroxyl, alkoxy, ketone, aldehyde, carboxylic acid, thiol, amide, sulfonate, sulfonic acid, sulfonamide, phosphonate, phosphoric acid group or a combination thereof, optionally substituted with one or more substituents selected from the same group as R1 and/or a halogen such as F, Cl, Br or I;

R' is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroalkenyl, substituted heteroalkenyl, heteroalkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocycloalkyl, substituted heterocycloalkyl, heterocycloalkenyl or substituted heterocycloalkenyl;

RI and/or R2 optionally forming a fused ring together with any of F, (X)_n or a part of (X)_n G, (Y)_m or a part of (Y)_m or RI and R2 themselves forming a fused ring;

X and Y are the same or different and have the same meaning as R' such as, e.g., -CH₂-, -CH₂-CH₂-, -CH₂-S-CH₂-, -CH₂-N-CH₂-, -CH₂-CH=CH-, -(CH₂)_d-(Z)_e-(V)_f-(W)_g(CH₂)_h-, -CH₂-O-CH₂-, wherein each of Z and W are independently C, S, O, N, Se or P and

V is -CH- or -CH₂-; (X), and/or (Y)_m optionally being substituted with one or more substituents selected from the same group as RI and/or a halogen such as F, Cl, Br or I;

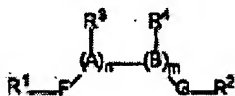
n is 0 or an integer of 1-5,

m is 0 or an integer of 1-5,

and/or g are an integer of 1-3,

d, f and/or h are an integer of 1-7.

Claim 57. (original) A drug discovery process according to claim 56, wherein the test compound has the general formula II



wherein F, G, R¹ and R² have the same meaning as in claim 56, R³ and R⁴ have the same meaning as R¹ and/or R², and A and B have independently the same meaning as X and Y in formula I. n and m have the same meaning as in formula I except that n and m may be 0 at the same time and then the basic structure is



and when n or m are 0, respectively, then the basic structures of formula II are



Claim 58. (original) A drug discovery process according to claim 57, wherein F and/or G is nitrogen (N) and/or oxygen (O) and the test compound has the general formula III, IV, V, VI or VII:



IIIA



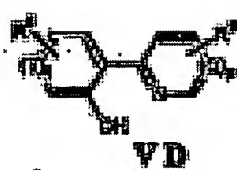
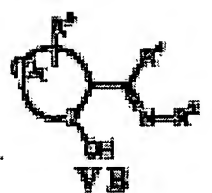
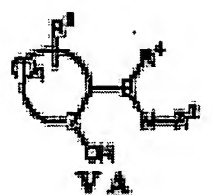
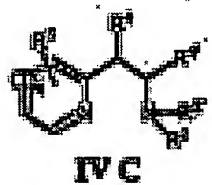
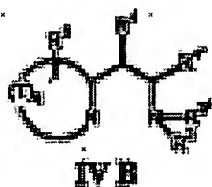
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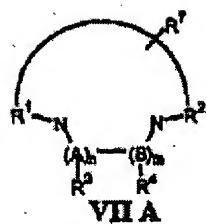


IIIC-G



IV A





wherein T and Q are heteroatoms, and q and s independently are 0 or an integer of from 1 to 4;

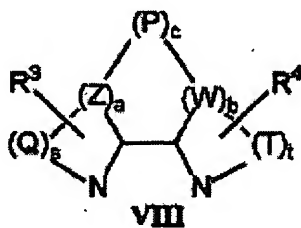
the meanings of q and s for q and/or s being 0 are the same as in Formula II for n and m;

a circle indicates a fused alkyl, alkenyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl or heteroaryl ring having from 3-7 atoms in the ring;

R5 has the same meaning as R1 and/or R2;

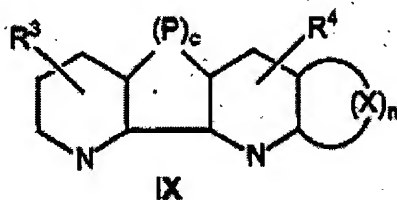
and in Formulas IIr C-G, IV C and V C-I), T and/or Q may be placed anywhere in the cyclic system.

Claim 59. (original) A drug discovery process according to claim 58, wherein the test compound has the general formula VIII



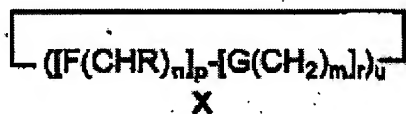
wherein R³, R⁴, Z, W and P are as defined herein before, a and/or b are an integer of 1-7 and c is 0 or an integer of 1-7, and each of Q and T is independently -CH- or -CH₂ s is an integer of 1-7, and t is an integer of 1-7, are believed to be particularly suitable; when c is 0 in the above Formula VIII then (P)_c- is absent, i.e. there is no bond between (Z)_a and (W)_b.

Claim 60. (original) A drug discovery process according to claim 56, wherein the test compound has the general formula IX



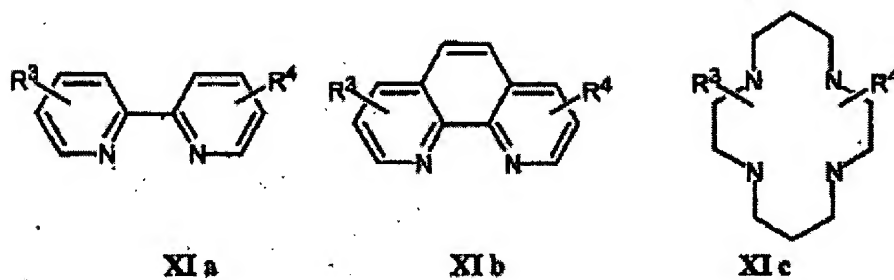
wherein R³, R⁴, F, X and n are as indicated above, and r is 0 or an integer of 1-3, and when r is 0 then -(P)_r- is absent.

Claim 61. (original) A drug discovery process according to claim 56, wherein the test compound has the general formula X



wherein F is N,O or S and G is N,O or S. n is an integer from 1 to 5,
m is 0 or an integer from 1 to 5,
p and/or r are 0 or an integer from 1 to 8, u is an integer from 1 to 8, and
R has the same meaning as R¹ in Formula I.

Claim 62. (original) A drug discovery process according to claim 56, wherein the test compound has the general formula XI



wherein R³ and R⁴ are as indicated above in formula I.

Claim 63. (previously presented) A drug discovery process according to claim 53, wherein the metal ion is one that binds to an amino acid residue containing a S, O, N, Se and/or P atom or with an aromatic amino acid residue.

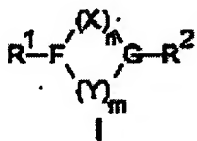
Claim 64. (original) A drug discovery process according to claim 63, wherein the amino acid residue is selected from the group consisting of Ser, Lys, Arg, Tyr, Thr, Trp, Phe, Asp, Glu, Asn, Gln, Cys and His, in particular Asp, Glu, Cys and His, preferably His.

Claim 65. (previously presented) A drug discovery process according to claim 53, wherein the metal ion is selected from the group consisting of aluminium, antimony, arsenic, astatine, barium, beryllium, bismuth, boron, cadmium, calcium, cerium, cesium, chromium, cobalt, copper, dysprosium, erbium, europium, gadolinium, gallium, germanium, gold, hafnium, holmium, indium, iridium, iron, lanthanum, lead, lutetium, magnesium, manganese, mercury, molybdenum, neodymium, nickel, niobium, osmium, palladium, platinum, polonium, praseodymium, promethium, rhenium, rhodium, rubidium, ruthenium, samarium, scandium, selenium, silicon, silver, strontium, tantalum, technetium, tellurium, terbium, thallium, thorium, thulium, tin, titanium, tungsten, vanadium, ytterbium, yttrium, zinc, zirconium, and oxidation states and isotopes thereof; in particular aluminium, antimony, barium, bismuth, calcium,

chromium, cobalt, copper, europium, gadolinium, gallium, germanium, gold, indium, iron, lutetium, manganese, magnesium, nickel, osmium, palladium,, platinum, rhenium, rhodium, rubidium, ruthenium, samarium, silver, strontium, technetium, terbium, thallium, thorium, tin, yttrium, zinc, and oxidation states or isotopes thereof; in particular cobalt, copper, nickel, platinum, ruthenium, and zincc, and oxidation states and isotopes thereof; preferably calcium (II), cobalt (II) and (III), copper (I) and (II), europium all), iron (II) and (III), magnesium (II), manganese (II), nickel (II) and (III), palladium (II), platinum (II) and (V), ruthenium (II), (III), (IV), (VI) and (VIII), samarium (III), terbium (III), zinc (II), or isotopes thereof, preferably cobalt al) and (III), copper (I) and (II), nickel (II) and (III), zinc (II) and platinum (II) and (V), or isotopes thereof.

Claim 66. (previously presented) A drug discovery process according to claim 53, wherein the test compound is a chelate like e.g. metal ion-phenanthroline complex, metal ion-bipyridyl complex and metal ion-1,4,8,11-tetraazacyclotetradecane complex such as, e.g., a Cu²⁺-phenanthroline complex, a Zn²⁺-phenanthroline complex, a Cu²⁺-bipyridyl complex, a Zn²⁺-bipyridyl complex, a Ca²⁺-bipyridyl complex, a Cu²⁺-1,4,8,11-tetraazacyclotetradecane, a Zn²⁺-1,4,8,11-tetraazacyclotetradecane.

Claim 67. (original) A chemical library comprising a plurality of test compounds of the following general formula I



wherein F is N, O, S, Se or P; and G is N, O, S, Se or P;

at least one of (X)_n and (Y)_m is present and if n is 0, then -(X)_n - is absent, and if m is 0, then -(Y)_m - is absent, and both n and m are not 0;

R1 and R2, which are the same or different, are radicals preferably selected from the group consisting of: hydrogen, a C1-C15 alkyl, C2-C15 alkenyl, C2-C15 alkynyl, aryl, cycloalkyl, alkoxy, ester, -OCOR COOR', heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl or heteroaryl group, an amine, imine, nitro, cyano, hydroxyl, alkoxy, ketone, aldehyde, carboxylic acid, thiol, amide, sulfonate, sulfonic acid, sulfonamide, phosphonate, phosphonic acid group or a combination thereof, optionally substituted with one or more substituents selected from the same group as R1 and/or a halogen such as F, Cl, Br or I;

R' is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroalkenyl, substituted heteroalkenyl, heteroalkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocycloalkyl, substituted heterocycloalkyl, heterocycloalkenyl or substituted heterocycloalkenyl;

R1 and/or R2 optionally forming a fused ring together with any of F, (X)_n or a part of (X)_n G, (Y)_m or a part of (Y)_m or R1 and R2 themselves forming a fused ring; X and Y are the same or different and have the same meaning as R' such as, e.g., -CH₂-, -CH₂-CH₂-, -CH₂-S-CH₂-, -CH₂-N-CH₂-, -CH=CH-CH-CH-, -(CH₂)_d-(Z)_e-(V)_f(W)_g-(CH₂)_h-, -CH₂-O-CH₂-, wherein

each of Z and W are independently C, S, O, N, Se or P and

V is -CH- or -CH₂-;

(X)_n and/or (Y)_m optionally being substituted with one or more substituents selected from the same group as R1 and/or a halogen such as F, Cl, Br or I;

n is 0 or an integer of 1-5,

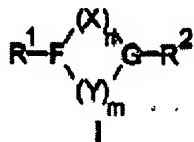
m is 0 or an integer of 1-5,

e and/or g are an integer of 1-3,

d, f and/or h are an integer of 1-7,

the test compounds being in the form of chelates formed between the test compound and a metal ion or atom selected from the group consisting of aluminium, antimony, arsenic, astatine, barium, beryllium, bismuth, boron, cadmium, calcium, cerium, cesium, chromium, cobalt, copper, dysprosium, erbium, europium, gadolinium, gallium, germanium, gold, hafnium, holmium, indium, iridium, iron, lanthanum, lead, lutetium, magnesium, manganese, mercury, molybdenum, neodymium, nickel, niobium, osmium, palladium, platinum, polonium, praseodymium, promethium, rhenium, rhodium, rubidium, ruthenium, samarium, scandium, selenium, silicon, silver, strontium, tantalum, technetium, tellurium, terbium, thallium, thorium, thulium, tin, titanium, tungsten, vanadium, ytterbium, yttrium, zinc, zirconium, and oxidation states and isotopes thereof; in particular aluminium, antimony, barium, bismuth, calcium, chromium, cobalt, copper, europium, gadolinium, gallium, germanium, gold, indium, iron, lutetium, manganese, magnesium, nickel, osmium, palladium, platinum, rhenium, rhodium, rubidium, ruthenium, samarium, silver, strontium, technetium, terbium, thallium, thorium, tin, yttrium, zinc, and oxidation states or isotopes thereof; in particular cobalt, copper, nickel, platinum, ruthenium, and zinc, and oxidation states and isotopes thereof preferably calcium (II), cobalt (II) and (III), copper (I) and (II), europium (III), iron, (II) and (III), magnesium (II), manganese (II); nickel (II) and (III), palladium, (II), platinum (II) and (V), ruthenium (II), (III), (IV), (VI) and (VIII), samarium (III), terbium (III), zinc (II), or isotopes thereof, preferably cobalt (II) and (III), copper (I) and (II), nickel (II) and (III), zinc (II) and platinum (II) and (V), or isotopes thereof.

68. (original) A chemical library comprising a plurality of test compounds of the following 15 general formula I



wherein F is N, O, S, Se or P; and G is N, O, S, Se or P;

at least one of (X)_n and (Y)_m is present and if n is 0, then -(X)_n - is absent, and if m is 0, then -(Y)_m - is absent, and both n and m are not 0;

R₁ and R₂, which are the same or different, are radicals preferably selected from the group consisting of: hydrogen, a C₁-C₅ alkyl, C₂-C₁₅ alkenyl, C₂-C₁₅ alkynyl, aryl, cycloalkyl, alkoxy, ester, -OOR', heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl or heteroaryl group, an amine, imine, nitro, cyano, hydroxyl, alkoxy, ketone, aldehyde, carboxylic acid, thiol, amide, sulfonate, sulfonic acid, sulfonamide, phosphonate, phosphonic acid group or a combination thereof, optionally substituted with one or more substituents selected from the same group as R₁ and/or a halogen such as F, Cl, Br or I;

R' is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroalkenyl, substituted heteroalkenyl, heteroalkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocycloalkyl, substituted heterocycloalkyl, heterocycloalkenyl or substituted heterocycloalkenyl;

R₁ and/or R₂ optionally forming a fused ring together with any of F, (X)_n or a part of (X)_n, (Y)_m or a part of (Y)_m or R₁ and R₂ themselves forming a fused ring; X and Y are the same or different and have the same meaning as R' such as, e.g., -CH₂-, -CH₂-CH₂-, -CH₂-S-CH₂-, -CH₂-N-CH₂-, -CH-CH-CH=CH-, -(CH₂)_d-(Z)_e-(Y)_f-(W)_g-(CH₂)_h-, -CH₂-O-CH₂-, wherein each of Z and W are independently C, S, O, N, Se or P and V is -CH- or -CH₂-; (X)_n and/or (Y)_m optionally being substituted with one or more substituents selected from the same group as R₁ and/or a halogen such as F, Cl, Br or I;

n is 0 or an integer of 1-5,
m is 0 or an integer of 1-5,
e and/or g are an integer of 1-3,
d, f and/or h are an integer of 1-7,

the test compounds being in non-chelated form.

Claim 69. (original) A chemical library comprising a plurality of metal ions selected from the group consisting of aluminium, antimony, arsenic, astatine, barium, beryllium, bismuth, boron, cadmium, calcium, cerium, cesium, chromium, cobalt, copper, dysprosium, erbium, europium, gadolinium, gallium, germanium, gold, hafnium, holmium, indium, iridium, iron, lanthanum, lead, lutetium, magnesium, manganese, mercury, molybdenum, neodymium, nickel, niobium, osmium, palladium, platinum, polonium, praseodymium, promethium, rhenium, rhodium, rubidium, ruthenium, samarium, scandium, selenium, silicon, silver, strontium, tantalum, technetium, tellurium, terbium, thallium, thorium, thulium, tin, titanium, tungsten, vanadium, ytterbium, yttrium, zinc, zirconium, and oxidation states and isotopes thereof; in particular aluminium, antimony, barium, bismuth, calcium, chromium, cobalt, copper, europium, gadolinium, gallium, germanium, gold, indium, iron, lutetium, manganese, magnesium, nickel, osmium, palladium, platinum, rhenium, rhodium, rubidium, ruthenium, samarium, silver, strontium, technetium, terbium, thallium, thorium, tin, yttrium, zinc, and oxidation states or isotopes thereof; in particular cobalt, copper, nickel, platinum, ruthenium, and zinc, and oxidation states and isotopes thereof, preferably calcium (II), cobalt (II) and (III), copper (I) and (II), europium (III), iron (II) and (III), magnesium (II), manganese (II), nickel (II) and (III), palladium (II), platinum (II) and (IV), ruthenium (II), (III), (IV), (VI) and (VIII), samarium (III), terbium (III), zinc (II), or isotopes thereof, preferably cobalt (II) and (III), copper (I) and (II), nickel (II) and (III), zinc (II) and platinum (II) and (IV), or isotopes thereof.

Claim 70. (previously amended) A chemical library according to claim 67, wherein the molecular weight of the individual test compounds is at the most 2000, log P is at the most 7, the number of hydrogen bond donors is at the most 10 and the number of hydrogen bond acceptors is at the most 15.

Claim 71. (original) A chemical library according to claim 70, wherein the molecular weight of the individual test compounds is at the most 1500 such as, e.g., at the most 1000 or at the most 500; log P is at the most 6 such as, e.g., at the most 5; the number of hydrogen bond donors is at the most 8 such as, e.g., at the most 7, 6 or 5; and the number of hydrogen bond acceptors is at the most 13 such as, e.g., 12, 11 or 10.

Claim 72. (previously presented) A chemical library according to claim 67 for using a drug discovery process according to claim 1.

Claim 73. (previously presented) Use of a test compound according to claim 53 in chelated form as either a stabilizing or as a destabilizing agent for di- or oligomerisation of a 5 biological target molecule.

Claim 74. (original) Use according to claim 73, wherein the biological target molecule is a membrane protein.

Claim 75. (original) Use according to claim 74, wherein the membrane protein is 7TM.

Claim 76. (original) Use of a test compound according to claim 53 in pharmacological knock-out experiments employing a biological target molecule in which a silent metal ion binding site has been created without affecting the binding action of an endogenous ligand for the biological target molecule with an aim of determining the effect of either an agonist or an antagonist on the physiological function of the metal ion site engineered receptor introduced into an animal by homologous gene replacement.

Claim 77. (original) A method for characterizing an orphan receptor, the method comprising

(a) mutating the orphan receptor in such a way that at least one amino acid residue capable of binding a metal ion is introduced into the orphan receptor so as to obtain a metal ion binding site as an anchor point in the mutated orphan receptor,

(b) contacting the mutated orphan receptor with a test compound which comprises a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of the test compound to the introduced metal ion binding site of the orphan receptor, and

(c) monitoring the binding of the test compound to the mutated orphan receptor by e.g. functional assays or through ligand binding assays.

Claim 78. (original) A method according to claim 77 further comprising an optimization step in order to improve the affinity of the test compound.

Claim 79. (original) Use of a test compound according to claim 53 as tracers in binding assays for orphan receptors.